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Ablation Strategies for Locally Advanced Pancreatic Cancer

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Key Words
Locally advanced pancreatic cancer · Ablation · Irreversible electroporation

Abstract
With the advent of novel and somewhat effective chemotherapy against pancreas cancer, several groups developed a new interest on locally advanced pancreatic cancer (LAPC). Unresectable tumors constitute up to 80% of pancreatic cancer (PC) at the time of diagnosis and are associated with a 5-year overall survival of less than 5%. To control those tumors locally, with perhaps improved patients survival, significant advances were made over the last 2 decades in the development of ablation methods including cryoablation, radiofrequency ablation, microwave ablation, high intensity focused ultrasound and irreversible electroporation (IRE). Many suggested a call for caution for possible severe or lethal complications in using such techniques on the pancreas. Most fears were on the heating or freezing of the pancreas, while non-thermal ablation (IRE) could offer safer approaches. The multimodal therapies along with high-resolution imaging guidance have created some enthusiasm toward ablation for LAPC. The impact of ablation techniques on primarily non-resectable PC remains, however, unclear.

Introduction

Pancreatic cancer (PC) is a dismal disease associated with a poor prognosis and a 5-year survival rate <10% for all stages, despite multimodal therapy [1]. The main factors for the lethal outcome are not only that most patients suffer from a primarily locally unresectable tumor or with metastatic disease at the time of diagnosis, but that many candidates for surgery do not benefit from a R0 resection [1]. A subgroup of these patients, who might benefit from locoregional therapies, are those with unresectable locally advanced PC (LAPC).

LAPC is characterized by the absence of distant metastases combined with complex tumor surrounding vessels, which either drastically complicates the resection or makes the resection approach impossible. According to the most common definitions, LAPC can be divided into borderline resectable (<10% of PC) and unresectable stages (20–30% of PC) [1, 2]. Whereas reported median survival reaches approximately 18 months for borderline resectable LAPC, unresectable LAPC shows reduced survival expectations of 9–13 months [3]. The heterogeneous

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Table 1. LAPC concept

Borderline resectable [4, 5]	Unresectable LAPC [4, 5]
Absence of distant metastases	
Involvement of SMV or PV No encasement of nearby arteries Proximal and distally free vessel	Involvement of SMV or PV Unreconstructable vein occlusion
Gastroduodenal artery encasement No extension to the celiac axis	Encasement of celiac artery >180°
Encasement of SMA <180°	Encasement of SMA >180°
Local lymph node metastases	Distant lymph nodes metastases

SMA = Superior mesenteric artery.

definitions of LAPC prevent any conclusive comparisons among different groups. The most popular classification systems are the American Hepato-Pancreato-Biliary Association (AHPBA) [4], the National Comprehensive Cancer Network (NCCN) guidelines [5] and MD Anderson [6] classification (table 1). The AHPBA classification is based on the extent of the tumor-vascular involvement and the NCCN guidelines adopted this classification providing a definition of LAPC based on radiological characteristics describing the tumor-surrounding vessel involvement [7]. In contrast, the MD Anderson classification extended the criteria of vessel involvement to patient-related characteristics. This system results in 3 classification subgroups as follows: Group A – radiological tumor arterial abutment or encasement or short-segment occlusion of the superior mesenteric vein (SMV), portal vein (PV) or PV-SMV; Group B – lesions suggestive for metastases; Group C – comorbidities requiring further workup and performance status of the patient [8].

High diagnostic accuracy is mandatory for proper therapeutic decision-making and distinction between resectable, borderline resectable and unresectable tumors. The diagnostic armamentarium includes contrast-enhanced CT, MRI, transcutaneous and endoscopic ultrasound (EUS) [9]. Multiphase contrast-enhanced CT enables 3-dimensional reconstruction of the pancreas and associated vascular structures. A histological analysis should be obtained by EUS-guided fine-needle biopsy [7]. In selected cases, diagnostic laparoscopy or laparotomy is used to exclude peritoneal metastases.

The current standard of care for unresectable LAPC is limited to chemotherapy alone or combined with chemoradiotherapy. Initial reports about gemcitabine monotherapy [10] or combination therapy [11] for unresectable LAPC provided disappointing response rates in the vicinity of 10%, whereas latter studies using gemcitabine-based combination regimes revealed higher response rates of approximately 25% [12–15]. This positive evolution in response rates, however, did not significantly translate into improved survival; median survival remained poor (<10 months) [13, 16]. Furthermore, encouraging results of the PRODIGE trial in 2011 [17] opened the door for the folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) regime, as a new effective chemotherapeutic strategy for metastatic or unresectable LAPC. Of importance, convincing trials investigating the efficacy of FOLFIRINOX in unresectable LAPC patients are missing up to date. Only retrospective analyses and a review of the literature postulate response rates between 35 and 40% with disease control rates of over 80% [18–21].

Several chemoradiotherapy combinations have been investigated as a treatment option for unresectable LAPC. Patients treated with gemcitabine-based chemoradiation protocols showed median survival from 11 to 15 months [22, 23]. The recent SCALOP study reported a survival benefit for orally administered 5-FU (capecitabine) based chemoradiation regimen, as compared with gemcitabine plus radiation (15 vs. 13 months, $p = 0.012$) [24]. Future perspectives for unresectable LAPC include a combination of FOLFIRINOX and radiation. Although evidence is anecdotal, initial reports postulate the feasibility of this approach [25, 26].

Despite the aforementioned advances in chemotherapy and chemoradiotherapy regimen, LAPC remains a disease with dismal prognosis. Locoregional ablative strategies for LAPC, delivered either intraoperatively, percutaneously or through EUS guidance, have evolved

on the knowledge gathered with tumors arising in other organs, which are routinely treated with these techniques.

A heterogeneous armamentarium of locoregional ablative therapeutic options has been described for unresectable solid organ malignancies. Liver tumors are an example where ablative strategies have been safely used for a long time. The pancreas, however, entails the risk of complications of associating injuries, especially the duodenum and major vessels. This led to delayed implementation of ablative techniques in LAPC with improving results over time. Local ablation was shown to palliate therapy-resistant pain and prolong survival by locally controlling the tumor burden as an additive to chemo or chemoradiotherapy. According to the energy applied, thermal- and non-thermal ablative techniques can be distinguished [27, 28]. This review mainly focuses on the role of ablative treatment in LAPC patients with emphasis on non-thermal ablation.

Ablation Therapy for LAPC

Thermal Ablation

Radiofrequency Ablation

Radiofrequency ablation (RFA) is the most common thermal ablation therapy used for LAPC. This approach is typically performed intraoperatively, with very little experience percutaneously. Briefly, radiofrequency causes tissue destruction by using heat (usually >40°C) generated from high frequency alternating current and exerts its effect via coagulation and protein denaturation [29, 30].

Although suggesting a survival benefit in up to 20 months [31] compared to 13 months in patients receiving standard chemotherapy alone, this treatment inherently entails the risk of thermal injuries to adjacent structures and pancreatic fistulae. Initial experiences translating this technique from animal studies into human revealed a morbidity rate up to 40% [32]. In the study by Wu et al. [33], the mortality rate reached 25%, whereas 3 quarters of these patients died from massive gastrointestinal hemorrhage after pancreatic head tumor ablation. Other centers demonstrated a wide range of mortality and morbidity rates [34–36] down to 3% mortality and 15% RFA-related morbidity [37] (table 2). Overall, PV thrombosis is the most frequent complication (15%) while duodenal injury seems to be the most threatening complication (8%) [37]. These injuries can range from asymptomatic mucosal burns to penetrating ulcers with massive bleeding requiring immediate surgical treatment. Girelli et al. [37] reported in 2013 the technical tips for improving RFA outcomes in LAPC: (a) avoiding temperatures over 90°C and (b) preventing high temperatures to diffuse to healthy surrounding tissues by not ablating the total tumor volume. These aspects may allow creating a 'safety margin' for temperature-associated tissue destruction. When such considerations were applied, the results shifted to lower complication rates (15%) and a progression-free survival rate of 22% at a median follow-up of 12 months [37] (fig. 1). A most recent study showed safety and feasibility of RFA under EUS guidance in 22 patients. The median post-ablation survival time was 6 months. Except one patient suffering from minor gastrointestinal bleeding not requiring further treatment, complications were related only to tumor progression [38].

Chemotherapy alone or combined chemoradiotherapy has an important role in the treatment of LAPC; however, there is currently little evidence to give recommendations on how to combine ablation therapy with chemotherapy or chemoradiation. For example, Girelli et al. [37] presented a retrospective study with 100 pancreatic RFA ablations in the context of a multimodal approach (fig. 1). In this study, the majority of cases (48%) were treated first by RFA followed by chemoradiotherapy, 29% received different chemotherapy regimen prior to RFA with chemoradiotherapy after ablation, 17% received chemoradiotherapy before and after RFA and 6% underwent different approaches, including intra-arterial chemotherapy, overall resulting in a median disease-free survival of 23 months [37]. Evidence regarding whether chemotherapy alone or chemoradiation should be offered before RFA, after RFA or both is still insufficient, and new study protocols are necessary to address these questions.

Microwave Ablation

Microwave (MW) ablation is performed by a generator using MW energy via an antenna to induce tissue heating of the area of interest. Major difference between MW ablation and RFA is the frequency range of the electromagnetic waves resulting in a better predictable ablation volume [39]. MW ablation results in coagulative tissue necrosis and is an established ablative method for unresectable malignant liver tumors. However, the experience of MW ablation for unresectable LAPC is limited. The largest case series [40] comprises 15 patients in which all partial necrosis was achieved with no major procedure-related morbidity or mortality. The longest patient follow-up was 22 months [40, 41]. Despite encouraging results, MW ablation for LAPC as well as its efficacy together with chemoradiotherapy is under in-

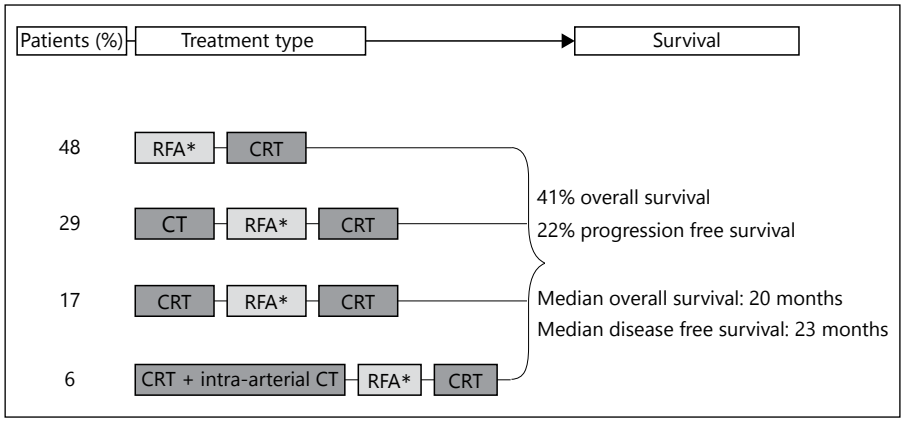

Fig. 1. RFA treatment for LAPC. CT = Chemotherapy; CRT = chemoradiotherapy.

Table 2. RFA outcome in LAPC

Year	Author	Indication	Study	n	Mode	Primary outcome	Results	Complications
2013	Giardino et al. [34]	LAPC	Retrospective observational	107	Intraoperative	OS	RFA: 14.7 months RFA + CRT: 25.6 months	Mortality: 1.8% Morbidity: 28%
2013	Figueroa-Barojas et al. [35]	LAPC	Retrospective observational	57	Intraoperative	OS DFS	OS and DSS: 19 months	Mortality: 0% Morbidity: 3.5%
2013	Girelli et al. [37]	LAPC	Prospective cohort	100	Intraoperative	OS PFS at 1 year	OS at 1 year: 41% PFS at 1 year: 22%	Mortality: 3% Morbidity: 24%
2012	Arcidiacono et al. [38]	LAPC	Prospective cohort	22	EUS guided	Safety Feasibility	Feasible: 72.8%	Pain: 13.6%
2010	Girelli et al. [32]	LAPC	Prospective cohort	50	Intraoperative	Safety Feasibility	–	Morbidity: 24%
2007	Spiliotis et al. [31]	LAPC, stage IV	Retrospective observational	16	Intraoperative	OS	OS: 33 months	Mortality: 0% Morbidity: 16%
2006	Wu et al. [33]	LAPC	Retrospective observational	16	Intraoperative	Pain relief	50% pain relief	Mortality: 25% Pancreatic fistula: 18.8%
2000	Matsui et al. [36]	LAPC, stage IV	Restrospective observational	29	Intraoperative	OS	OS: 3 months	Mortality: 10%

DFS = Disease-free survival; PFS = progression-free survival; CRT = chemoradiotherapy.

vestigation without any conclusive data currently available regarding indication and best ablation protocol for LAPC.

Cryoablation

Cryoablation was first described in a primate model in the 1970s [42] and was thereafter used for other tumor entities as hepatocellular carcinoma before the indication for PC ablation [43]. This procedure cools the tumor until ice ball formation occurs, leading then to tumor necrosis. Ideally, this ice ball engulfs and destroys the tumor while sparing healthy tissue. Cryoablation for LAPC is reported mostly in retrospective case series. This therapy presents complication rates ranging from 0 to 40% [44, 45] having the most severe bleeding from the puncture site or cracking of the liver, pancreatitis and overall sur-

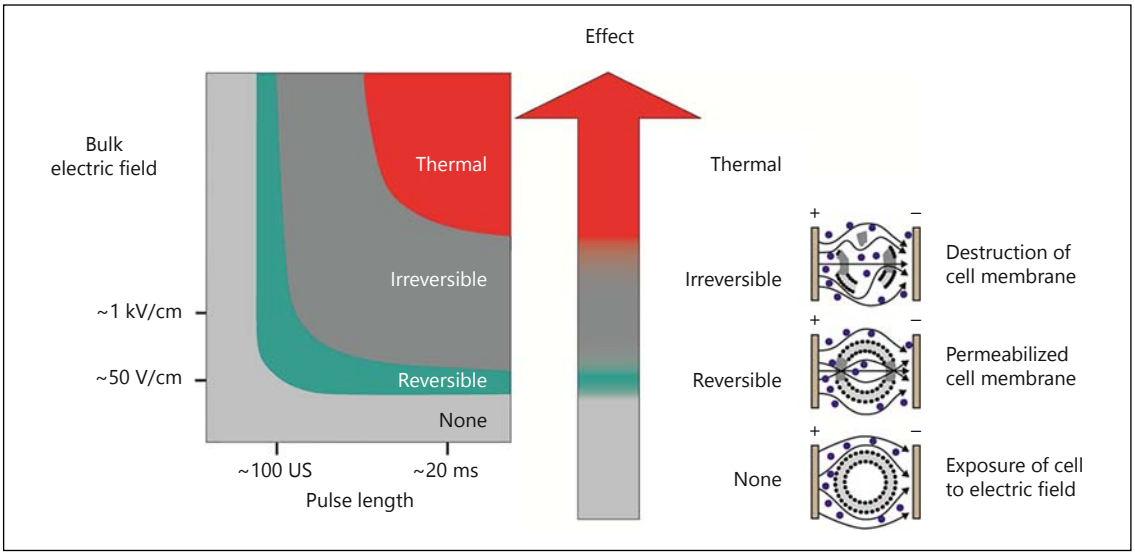

Fig. 2. Electroporation effects on the cellular membrane. This figure was adopted from Bower et al. [53].

vival (OS) rates between 12 and 30 months [45, 46]. Currently, this type of ablation technique seems to be abandoned for LAPC.

High Intensity Focused Ultrasound

High intensity focused ultrasound (HIFU) is an emerging ultrasound (US)-based system causing thermal tissue destruction, when boiling bubbles disrupt the tissue mechanically [47]. High amplitude pressure waves focused on very small regions exert this effect thereby sparing the intervening tissue. This highly focused therapy requires high resolution imaging techniques, essentially diagnostic US or MRI to safely guide HIFU. A recent study on HIFU in stages III and IV PC included 30 patients achieving a partial treatment response in 4 patients and local disease control in 22 patients. Adverse events occurred in 10% of the cases as pancreatic pseudocyst formation and mild pancreatitis. New developments include, for example, miniaturized HIFU capable for minimally invasive HIFU ablation, either laparoscopically or percutaneously [48].

In summary, thermal ablation therapy aims to relieve pain and prolong survival via local tumor control. These various techniques do have unique advantages and disadvantages making them more or less suitable in different situations [49]. However, the best treatment modality, as well as the sequential combination with chemotherapy and chemoradiotherapy, was investigated only in small, non-randomized clinical studies, keeping the question open as to how to improve survival rates in unresectable LAPC-treated by thermal ablation.

Non-Thermal Ablation – IRE

Irreversible electroporation (IRE) is a new non-thermal ablation technique which has been recently used for LAPC [50]. Electroporation was introduced in the late 1950s with the demonstration that electric stimulation causes cell membrane disruption. This observation was further developed and later introduced in cancer therapy as reversible electroporation [51]. Then, reversible electroporation was initially used to enhance chemotherapy uptake in tumors by membrane permeabilization [52]. Afterwards, higher magnitude electric pulses caused irreversible nanopores in the cell membrane and consequently cell death [50, 53] (fig. 2). Importantly, this effect shows a molecular selectivity by only affecting the lipid bilayer of the cell membrane whereas thermal ablation techniques affect all molecules in the treated area [51].

IRE works when energy is applied by placing at least 2 needles (maximum 6) around the tumor tissue. Pulses of direct current (maximum 50 ampere) are delivered for 70 µs between the needles. For safety reasons, this delivery rate is synchronized to the heart rate (ECG triggered) resulting in one energy pulse per R-wave. Potential hazards when dealing with IRE are electrical harmonics that can cause cardiac arrhythmias or muscle contraction. Therefore IRE treatment can only be performed under general anesthesia and paralytic induction.

Major drawback inherent to all thermal ablation techniques is the fact that these therapies comprise the risk of heat-sink effect. This becomes particularly important, as the pancreas is an organ with a peculiar position, with

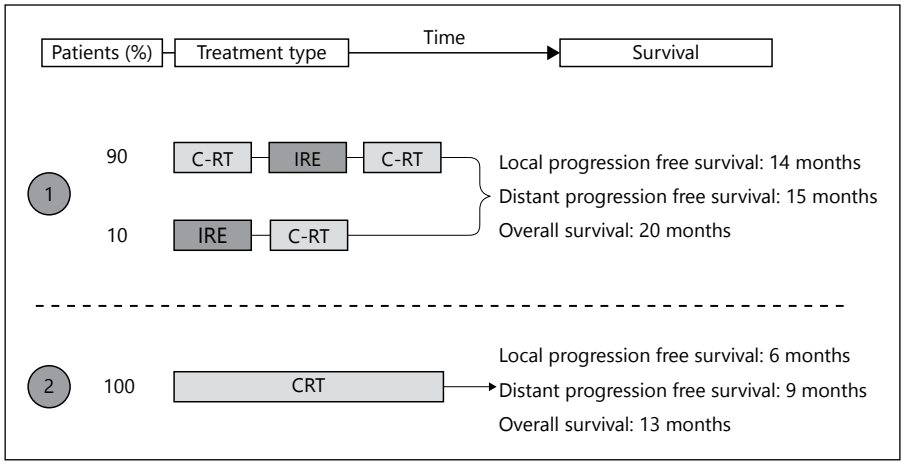

Fig. 3. Treatment approaches using IRE and chemoradiotherapy. C-RT = Chemo/chemoradiotherapy; CRT = chemoradiotherapy.

close relation to the duodenum, the bile duct and major vessels. This feature turned IRE into an attractive tool for LAPC ablation. Taking together that pathological studies revealed that a third of patients died of PC as a result of local tumor infiltration, without evidence for metastatic disease [54], this population appears to be ideal for IRE to increase patient survival and, importantly, quality of life.

A prospective, multi-institutional study included 54 patients comparing standard regimen of chemotherapy or chemoradiation with IRE [55]. Only patients with PC AJCC stage III criteria for LAPC were included in the study (70% primary of the pancreatic head, 30% primary of the pancreatic body). Ninety percent of the patients received chemotherapy or chemoradiation pre-IRE, while 10% received this treatment after IRE. Comparing this cohort to patients receiving standard treatment, an improvement of local progression-free survival (14 vs. 6 months), distant progression-free survival (15 vs. 9 months) and OS (20 vs. 13 months) was reported (fig. 3). Complications in the IRE group included bile leaks and duodenal leaks, 4% each, with 1 patient dying within 90 days after intervention. This study suggests a possible benefit in LAPC patient survival, when IRE is combined with chemotherapy and/or chemoradiation.

A registry-based study showed high rate of complications (42%) post-IRE for PC. However, only 19% were related to the procedure itself and with incomplete ablation in 2 cases. Another important point demonstrated in this study is the correlation of the learning curve to the rate of complications, which seems to drop after a cumulative experience of minimal 5 IRE cases in PC [56].

Among the small series of a percutaneous approach for IRE [57, 58], pancreatitis and pneumothorax were the most frequent complications, while the 6 months OS rate ranged from 40 to 70% (table 3). These studies focused mostly on feasibility and safety. However, longer follow-up is necessary to evaluate local recurrence rate using percutaneous IRE.

In addition to that, IRE has been described as a tool to increase the number of negative margins after pancreatectomy in borderline resectable PC, especially regarding the retroperitoneal margin [59]. Forty-eight patients eligible for resection were enrolled in this study, 25 borderline resectable and 23 LAPC. All patients underwent chemoradiotherapy according to local regimen before and after resection. Only 6% experienced local recurrence with a median survival of 22.4 months. Within 90 days, adverse events occurred in 38% of patients with 11% possibly related to IRE. Taking this together, margin accentuation by IRE is a new concept, which requires further investigation.

In our center, IRE for unresectable LAPC is indicated for tumors up to 4 cm in the anterior-posterior axis. Despite controversies, biliary metal stent or other material in the vicinity of the IRE ablation has been adopted as contraindication to perform IRE in LAPC. It is performed following induction chemotherapy and in the absence of metastases. Those patients undergo diagnostic laparoscopy at the time of the procedure and depending on individual indication, associated surgical procedures as choledocojejunostomy and gastrojejunostomy may be performed. This therapy was firstly applied by 90 pulses delivery, and most recently, modulated pulse delivery (meaning repeated sequence of fewer pulses) is preferred. All patients undergo chemotherapy after IRE treatment, and only in presence of local recurrence they undergo radiotherapy. Despite the procedure seeming to be safe, there are unknown important points regard-

Table 3. IRE outcome in LAPC

Year	Author	Indication	Study	n	Mode	Primary outcome	Results	Complications
2014	Mansson et al. [58]	LAPC	Phase 1	5	Percutaneous US-guided	Safety	6 months survival: 40% 30 days mortality: 0	Pancreatitis (n = 1)
2013	Philips et al. [56]	LAPC	Retrospective observational	59	Intraoperative	Safety	–	Morbidity: 42%
2013	Martin et al. [55]	LAPC	Prospective cohort	54	Intraoperative	OS PFS	OS for IRE and CT/RT: 20 months PFS for IRE and CT/RT: 15 months OS for CT/RT: 13 months PFS for CT/RT: 6 months	Morbidity in IRE and CT/RT: 22% Morbidity in CT/RT: 41%
2012	Narayanan et al. [57]	LAPC, stage IV	Retrospective observational	14	Percutaneous US-guided	Safety	6-month OS: 70%	Pancreatitis (n = 1) Pneumothorax (n = 1)

CT = Chemotherapy; RT = radiotherapy; PFS = progression-free survival.

ing the use of chemo or chemoradiotherapy, patient selection, type of imaging for follow-up and assessment of treatment success. Therefore, critical evaluation of IRE results is mandatory for better management of LAPC patients.

Image-Guided Percutaneous Ablation

Although percutaneous US- or CT-guided biopsy and fine needle aspiration of pancreatic lesions were established procedures for some time, percutaneous ablation of pancreatic tumors was perceived as neither feasible nor safe until recently. Indeed, in the vast majority of patients with LAPC reported hitherto, the applicators were inserted under US guidance intraoperatively (tables 2 and 3). Pancreas anatomical constraints may limit percutaneous applicator placement, while this may not be an issue at open approach. For instance, the presence of peri-pancreatic varices [57] or the lack of an US 'window' represents limitations to the percutaneous approach. On one hand, the open approach allows confirmation of tumor inoperability. On the other hand, a postoperative 'hostile' anatomy or severe comorbidity may be a reason to favor the less invasive percutaneous access. In 2 small series, the feasibility and safety of percutaneous US- or CT-guided percutaneous IRE has been shown [57, 58]. In a report of 5 patients, there were no immediate complications after percutaneous US-guided MW ablation performed with moderate sedation [41]. A single late complication, a pseudoaneurysm of the gastroduodenal artery, occurred after 1 month [41]. The published clinical experience in ablation for LAPC does not give us any hint yet regarding the choice of the ablative method, the best approach (open vs. percutaneous) or the type of imaging guidance. However, as techniques evolve continuously, percutaneous ablation therapy for LAPC may gain wider acceptance.

Conclusion

Ablative techniques for unresectable LAPC are a rapidly emerging field focusing on local tumor control. Currently, long-term data or randomized controlled trials are not available yet for any of the mentioned ablative treatments. In addition, the role of ablation therapy combined with chemotherapy or chemoradiotherapy, and the best therapy sequence is unclear. Most clinical ablative experience for LAPC exists with RFA. However, the high rate of complications of RFA for LAPC seems to be an important drawback. Conversely, IRE is gaining acceptance, proceeding fast from the experimental stage to clinical practice, but convincing data about effectiveness of IRE has not been published yet and a randomized control trial comparing IRE with standard therapy seems timely. Therefore, better survival rates in LAPC may be accomplished in the future by individualized patient treatment in a multidisciplinary approach with new emerging therapies.

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